

**IN THE UNITED STATES DISTRICT COURT  
FOR THE SOUTHERN DISTRICT OF INDIANA  
INDIANAPOLIS DIVISION**

ELI LILLY AND COMPANY,	)	
	)	
Plaintiff,	)	
	)	
v.	)	Civil Action No. 1:10-cv-01376-TWP-DKL
	)	
TEVA PARENTERAL MEDICINES, INC.,	)	
APP PHARMACEUTICALS, LLC,	)	<b>PUBLIC VERSION</b>
PLIVA HRVATSKA D.O.O.,	)	
TEVA PHARMACEUTICALS USA, INC., and	)	
BARR LABORATORIES, INC.,	)	
	)	
Defendants.	)	
_____	)	

**DEFENDANTS' PRE-TRIAL BRIEF REGARDING PLAINTIFF'S ALLEGATION OF  
INFRINGEMENT OF U.S. PATENT NO. 7,772,209**

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**Table of Abbreviations**

<b>Abbreviation</b>	<b>Document Description</b>
<b><u>General</u></b>	
“Teva”	Teva Parenteral Medicines, Inc. and Teva Pharmaceuticals USA, Inc.
“APP”	APP Pharmaceuticals, LLC
“Defendants”	Teva and APP
“Lilly” / “Eli Lilly”	Eli Lilly and Company
“Asserted Claims”	Claims 9, 10, 12, 14, 15, 18, 19, and 21 of the ’209 patent
“TX”	Trial Exhibit
“ANDA”	Abbreviated New Drug Application
“POSA”	Person of ordinary skill in the art
<b><u>Exhibits</u></b>	
“Briefing Document”	Briefing Document, (February 16, 2000) (TX 76; attached hereto in part)
“Chabner Rpt.”	January 8, 2013 Expert Report of Bruce A. Chabner, M.D. (TX 2250; attached hereto in part)
“Hammond”	Hammond, <i>et al.</i> , <i>A phase I and pharmacokinetic (PK) study of the multitargeted antifol (MTA) LY231514 with folic acid</i> , AMERICAN SOCIETY OF CLINICAL ONCOLOGY, 17: 225a Abstract 866 (1998) (TX 912; attached hereto)
“Lilly Amicus Brief”	Brief of Amicus Curiae Eli Lilly and Company, Supporting Respondents, <i>Limelight Networks, Inc. v. Akamai Techs., Inc.</i> , No. 12-786, 2014 WL 1319146 (U.S. Apr. 2, 2014) (attached as Exhibit A)
“Protocol JMCF(f) Amendment”	Letter from Lilly to FDA re IND 40,061, MTA (LY231514); Serial No. 291 Protocol H3E-MC-JMCH(f), dated February 6, 2001 (TX 336; attached hereto in part)

Abbreviation	Document Description
"Rusthoven"	Rusthoven, <i>et al.</i> <i>Multitargeted Antifolate LY231514 as a First-Line Chemotherapy for Patients With Advanced Non-Small-Cell Lung Cancer: A Phase II Study</i> , JOURNAL OF CLINICAL ONCOLOGY, 17(4): 1194-1199 (1999) (TX 78; attached hereto)
"Rusthoven Tr."	Excerpts from the October 2, 2012 deposition of James Rusthoven, M.D. (attached as Exhibit B)
"Shih"	Shih <i>et al.</i> , <i>Preclinical Pharmacology Studies and the Clinical Development of a Novel Multitargeted Antifolate, MTA (LY231514)</i> , ANTICANCER DRUG DEVELOPMENT GUIDE: ANTIFOLATE DRUGS IN CANCER THERAPY, (Jackman: Editor) Chapter 8:183-201 (1999) (TX 1152; attached hereto in part)
"the '209 patent / patent-in-suit"	U.S. Patent No. 7,772,209 (TX 1; attached hereto)

## **I. Introduction**

This short trial will address the question of whether Lilly can prove, by a preponderance of the evidence, that Teva or APP will infringe any of claims 9, 10, 12, 14, 15, 18, 19 and 21 of U.S. Patent No. 7,772,209. Each asserted claim is a method claim; because neither Teva nor APP directly treats any patient, Lilly has not asserted, and cannot assert, that any of these claims are directly infringed by Defendants. The question for trial will therefore be limited to whether Teva or APP induce or contribute to infringement by encouraging a single actor to directly infringe – *i.e.*, to carry out each and every step of – the asserted claims. As Lilly will be unable to demonstrate that any single actor directly infringes the claims, it will not be able to sustain its allegation that the Defendants indirectly infringe.

The asserted claims each require a method of administering pemetrexed after administering folic acid and vitamin B12. Properly understood, however, no single individual (or sufficiently related group of people) administers all three of the claimed treatments. Rather, a doctor (or affiliated staff) administers pemetrexed (intravenously) and vitamin B12 (by injection). But the patient administers folic acid, by taking an over-the-counter folic acid pill, or a multivitamin that contains folic acid. Because no individual carries out each step of the '209 patent method claims, those claims are not directly infringed. And as the Supreme Court has recently held, absent direct infringement, no party can be liable for indirect infringement. *Limelight Networks, Inc. v. Akamai Techs., Inc.*, 134 S. Ct. 2111, 2117 (2014). Judgment for Defendants is therefore required.

This issue was not tried during the prior trial before this Court because a different legal standard applied at the time. Previously, the law allowed a claim of induced infringement even if no single party directly performed each step of an asserted claim; rather, what mattered was whether a party induced the performance of all the steps of claim, no matter how many

independent actors were required to perform those steps. Lilly thus argued that Defendants induced the doctor and patient, in combination, to perform the steps of the asserted claims. But such a theory is no longer viable—the Supreme Court has expressly rejected it. In doing so, the Supreme Court was well aware of the implications for cases such as this one—Lilly itself explained to the Court that such a change in the law would adversely impact the ability of pharmaceutical companies to enforce patents with claims just like those asserted here.

Under current law, Lilly cannot rely upon the combined actions of the doctor and the patient. The actions of multiple actors can only be combined to show direct infringement if the doctor exercises specific direction or control over the patient by demonstrating an agency relationship or a contractual arrangement sufficient to establish that the physician is vicariously liable for the patient’s actions. This high standard of control cannot be met here. As both the Federal Circuit and Lilly have recognized, such direction or control does not exist in the relationship between a physician and his or her patient, who simply cooperate at arm’s length. Therefore, a finding of non-infringement is required.

## **II. Background**

### **A. Procedural History**

Teva and APP filed respective ANDAs with the FDA seeking approval to market generic versions of Lilly’s ALIMTA<sup>®</sup> products (collectively, “Defendants’ ANDA products”) prior to the expiration of the ’209 patent. Subsequently, Lilly sued Defendants for infringement of the ’209 patent, alleging that Defendants induce or contribute to infringement of the ’209 patent because the use of Defendants’ ANDA products in accordance with Defendants’ proposed labeling for each product would allegedly literally infringe one or more claims of the ’209 patent. *See* D.I. 1 at 29, 34, 46 51, 61 and 66. Since then, Lilly has stipulated that it is only asserting infringement of claims 9, 10, 12, 14, 15, 18, 19, and 21 of the ’209 patent. D.I. 233 at ¶ 2. Lilly

is not asserting direct infringement and has not presented any evidence of infringement under the doctrine of equivalents.

In response to Lilly's infringement allegations, Defendants argued that there could be no direct infringement of the '209 patent claims because in accordance with Defendants' proposed labeling, no single actor performed each and every step of the '209 patent claims. That historically meant no indirect infringement under 35 U.S.C. § 271(b) or (c) because direct infringement was a predicate for a finding of indirect infringement. *Joy Techs., Inc. v. Flakt, Inc.*, 6 F.3d 770, 774 (Fed. Cir. 1993) ("Liability for either active inducement of infringement or for contributory infringement is dependent upon the existence of direct infringement."). In its August 31, 2012 *en banc* decision in *Akamai*, however, the Federal Circuit stated that the law allowed a claim of induced infringement if all the steps of the claim were induced, no matter how many actors were required to perform those steps. *Akamai Techs., Inc. v. Limelight Networks, Inc.*, 692 F.3d 1301, 1307-09 (Fed. Cir. 2012) (*en banc*), *rev'd*, 134 S. Ct. 2111 (2014). Therefore, on June 14, 2013, Defendants conditionally stipulated to induced infringement of the '209 patent, assuming the claims were to be found valid and enforceable and based upon the law at the time concerning infringement. D.I. 233 at ¶ 3. However, as the possibility remained that the Supreme Court would revise the law, the parties agreed to hold a separate trial on the issue of infringement if that occurred. *Id.* at ¶ 4. Trial was held solely for the issue of invalidity in August 2013. On March 31, 2014, the Court found that the Defendants had not proven by clear and convincing evidence that the '209 patent was invalid, and thus entered an order against Defendants that they infringed the asserted claims of the '209 patent. D.I. 336; D.I. 337.

Since the original trial, the law on indirect infringement has changed. Specifically, the Supreme Court restored the rule that a finding of direct infringement is a predicate for a finding

of indirect infringement, and thus, indirect infringement requires that each of the steps of a claim must be performed by, or attributed to, a single actor. *Akamai*, 134 S. Ct. at 2117.

Consequently, the argument that Defendants induce the doctor and patient combined to perform the steps of the asserted claims according to their product labeling is no longer a viable theory for infringement. Subsequent to the Supreme Court's decision in *Akamai*, the parties took action to have the case remanded back to this Court for this trial on infringement. *See* D.I. 347.

### **B. The '209 Patent Claims**

Lilly is asserting only claims 9, 10, 12, 14, 15, 18, 19, and 21 of the '209 patent. All of these claims require the administration of three agents, (1) pemetrexed disodium, (2) folic acid, and (3) vitamin B12, to a "patient" in need thereof.<sup>1</sup> The Court has construed "patient" to be a "human undergoing medical treatment." D.I. 115 at 21.

Claim 1, from which claims 9 and 10 depend, reads:

A method for administering pemetrexed disodium to a patient in need thereof comprising

administering an effective amount of folic acid and an effective amount of a methylmalonic acid lowering agent

followed by administering an effective amount of pemetrexed disodium,

wherein the methylmalonic acid lowering agent is selected from the group consisting of vitamin B12, hydroxycobalamin, cyano-10-chlorocobalamin, aquocobalamin perchlorate, aquo-10-cobalamin perchlorate, azidocobalamin, cobalamin, cyanocobalamin, or chlorocobalamin.

TX 1 ('209 patent) at 10:55-65.<sup>2</sup> Claims 9 and 10 require that the methylmalonic acid lowering agent of claim 1 is vitamin B12 and specify the dose of folic acid administered in claim 1.

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<sup>1</sup> This Court previously held that the POSA with respect to the '209 patent can be a medical doctor who specializes in oncology or a medical doctor with extensive experience in the areas of nutritional sciences involving vitamin deficiencies. D.I. No. 336 at 9. However, as to the latter person, this individual would need to have collaborated with medical oncologists who have knowledge and experience in the treatment of cancer through the use of antifolates. *Id.*

<sup>2</sup> Trial Exhibits cited in this brief are attached in full hereto, unless otherwise noted in the Table of Abbreviations.

Claim 12 reads:

An improved method for administering pemetrexed disodium to a patient in need of chemotherapeutic treatment, wherein the improvement comprises:

- a) administration of between about 350 µg and about 1000 µg of folic acid prior to the first administration of pemetrexed disodium;
- b) administration of about 500 µg to about 1500 µg of vitamin B12, prior to the first administration of pemetrexed disodium; and
- c) administration of pemetrexed disodium.

*Id.* at 11:23-12:5. Asserted claims 14, 15, 18, 19, and 21 depend from claim 12 and further specify the dose, route, and schedule for administration of folic acid or vitamin B12.

### **C. The Defendants' Proposed Labeling Information**

As the parties agree, this case focuses on the proposed labeling that accompanies Defendants' ANDA products. D.I. 358 at ¶ 1. Defendants' ANDA products are generic equivalents of ALIMTA<sup>®</sup>, and thus, subject to certain exceptions, must have labeling that is "the same as the labeling approved for" ALIMTA<sup>®</sup>. *See* 21 U.S.C. § 355(j)(2)(A)(v). The labeling for ALIMTA<sup>®</sup> and Defendants' ANDA products consists of two parts: (1) prescribing information for physicians; and (2) information for patients. Over the last couple of years, Lilly has made minor revisions to both portions of the ALIMTA<sup>®</sup> labeling that Defendants have not yet incorporated into their proposed labeling. Because Defendants' proposed labeling will likely be modified to reflect these recent changes, to simplify the upcoming trial on infringement, the parties have agreed to treat the product labeling for ALIMTA as if it were Defendants' product labeling. *Id.* at ¶¶ 7-10. In this brief, and at trial, Defendants will cite and refer to excerpts from the ALIMTA<sup>®</sup> prescribing information (TX 3018) and patient information (TX 3017), as if it were referring to Defendants' proposed labeling.

**1. Pemetrexed And Vitamin B12 Will Be Administered By The Physician**

As directed by the Defendants' proposed labeling, the physician will administer the pemetrexed and vitamin B12. For example, the physician prescribing information states that pemetrexed is "administered as an intravenous infusion" and that vitamin B12 is administered "intramuscularly 1 week prior to the first dose of ALIMTA" as an intramuscular injection. TX 3018 at 2. The patient information informs the patient that the physician will administer these injections of pemetrexed disodium and vitamin B12 to the patient:

ALIMTA is slowly infused (injected) into a vein. The injection or infusion will last about 10 minutes. You will usually receive ALIMTA once every 21 days (3 weeks). TX 3017 at 1.

Your doctor will give you vitamin B<sub>12</sub> injections while you are getting treatment with ALIMTA. *Id* at 2.

Thus, as set forth in Defendants' proposed labeling, a physician (or affiliated staff), will administer pemetrexed and vitamin B12 to the patient.

**2. Folic Acid Will Be Administered By The Patient**

As directed by the proposed labels, however, the physician (or other medical professionals) will *not* administer folic acid. Rather, the patient will administer folic acid to him- or herself each day before, during and after receiving pemetrexed. For example, the prescribing information states:

Instruct patients to initiate folic acid 400 mcg to 1000 mcg orally once daily beginning 7 days before the first dose of ALIMTA. TX 3018 at 2.

The patient information indicates that it is up to the patient to select, obtain and administer folic acid:

It is very important to take folic acid and vitamin B12 during your treatment with ALIMTA to lower your chances of harmful side effects. You must start taking 400-1000 micrograms of folic acid every day for at least 5 days out of the 7 days before your first dose of ALIMTA. You must keep taking folic acid every day during the time you are getting treatment with ALIMTA and for 21 days after

your last treatment. ***You can get folic acid vitamins over-the-counter. Folic acid is also found in many multivitamin pills.*** Ask your doctor or pharmacist for help if you are not sure how to choose a folic acid product. TX 3017 at 2.

Thus, as set forth in Defendants’ proposed labeling, the patient should administer to him- or herself folic acid. There is no instruction for a physician to administer folic acid to the patient in the hospital or clinic, or even for the physician to prescribe folic acid—the label suggests that the patient should select a form and dose of folic acid, and purchase it over the counter. *See also* TX 3018 at 2 (stating that the doctor should “instruct patients to initiate folic acid . . . orally” and that the doctor should “administer vitamin B12 1 mg intramuscularly”).

### **III. Summary Of The Law On Infringement**

#### **A. Infringement Generally**

U.S. patent law recognizes two general types of infringement: direct infringement, under 35 U.S.C. § 271(a), and indirect infringement, which encompasses induced infringement under 35 U.S.C. § 271(b) and contributory infringement under 35 U.S.C. § 271(c).

The patent owner has the burden of proving by a preponderance of the evidence that every limitation of the patent claim asserted to be infringed is found in an accused method. *See SmithKline Diagnostics, Inc. v. Helena Labs. Corp.*, 859 F.2d 878, 889 (Fed. Cir. 1988).

Determining whether an accused method directly infringes a patent claim involves two steps: first, construction of the claim by the Court to determine its meaning and scope; and second, comparison of the claim as construed by the Court to the method at issue. *See Tanabe Seiyaku Co. v. U.S. Int’l Trade Comm’n*, 109 F.3d 726, 731 (Fed. Cir. 1997).

Direct infringement of a method claim generally requires the patent owner to prove that a single party performs every step of a claimed method. *Muniauction, Inc. v. Thomson Corp.*, 532 F.3d 1318, 1329 (Fed. Cir. 2008); *BMC Res., Inc. v. Paymentech, L.P.*, 498 F.3d 1373, 1378-79 (Fed. Cir. 2007). Where multiple actors perform all the steps of a claimed method, “the claim is

directly infringed **only** if one party exercises ‘control or direction’ over the entire process such that every step is attributable to the controlling party, *i.e.*, the ‘mastermind.’” *Muniauction*, 532 F.3d at 1329 (emphasis added). In other words, that “mastermind” must be considered vicariously liable for the other’s actions. *See Aristocrat Techs. Austl. Pty Ltd. v. Int’l Game Tech.*, 709 F.3d 1348, 1363 (Fed. Cir. 2013). This is a very strict standard, as the Federal Circuit has explained that absent a “**principal/agent relationship**” or “**like contractual relationship**” (or in other words, a “joint enterprise”), it has “declined to find one party vicariously liable for another’s actions.” *Id.* (emphasis added); *see Akamai*, 692 F.3d at 1307 (“**Absent an agency relationship between the actors or some equivalent**, however, a party that does not commit all the acts necessary to constitute infringement has not been held liable for direct infringement even if the parties have arranged to ‘divide’ their acts of infringing conduct for the specific purpose of avoiding infringement liability.”) (emphasis added). “[M]ere ‘arms-length cooperation’ will not give rise to direct infringement by any party.” *Muniauction*, 532 F.3d at 1329. The Federal Circuit acknowledged that this rule “may in some circumstances” allow parties to avoid infringement, but stated that this “concern does not outweigh concerns over expanding the rules governing direct infringement.” *BMC*, 498 F.3d at 1381.<sup>3</sup>

Absent direct infringement of the patent claims, there can be no indirect infringement. *Akamai*, 134 S.Ct. at 2117. In addition to direct infringement, to succeed on a claim of induced infringement, the patentee must show “that the alleged infringer knowingly induced infringement and possessed specific intent to encourage another’s infringement.” *MEMC Elec. Materials, Inc. v. Mitsubishi Materials Silicon Corp.*, 420 F.3d 1369, 1378 (Fed. Cir. 2005) (citation omitted).

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<sup>3</sup> The Court noted that “expanding the rules governing direct infringement to reach independent conduct of multiple actors would subvert the statutory scheme for indirect infringement,” because direct infringement is a strict-liability offense. *BMC*, 498 F.3d at 1381. Performing less than all of the elements is not infringement, and it would be inappropriate to hold a party strictly liable for such permissible activity.

The intent requirement for inducement requires the inducer to “have an affirmative intent to cause direct infringement.” *DSU Med. Corp. v. JMS Co.*, 471 F.3d 1293, 1306 (Fed. Cir. 2006) (en banc). Thus, the alleged infringer must have knowingly induced, with specific intent to encourage, a single actor to perform every step of a claimed method. *Akamai*, 134 S. Ct. at 2119. Moreover, to succeed on a claim of contributory infringement, the patentee must also show that there are no “substantial noninfringing use[s]” of the product sold by the accused infringer. 35 U.S.C. § 271(c); *Toshiba Corp. v. Imation Corp.*, 681 F.3d 1358, 1362 (Fed. Cir. 2012).

#### **B. Infringement In A Hatch-Waxman Litigation**

In this Hatch-Waxman litigation, the infringement question is “whether what the generic drug maker is requesting authorization for in the ANDA would be an act of infringement if performed.” *See Warner-Lambert Co. v. Apotex Corp.*, 316 F.3d 1348, 1364-65 (Fed. Cir. 2003). Where a method of treatment patent, like the ‘209 patent, is asserted, pharmaceutical companies cannot be liable for direct infringement because pharmaceutical companies do not actually administer drugs or treat patients. *Id.* at 1363, n.7. Instead, Defendants may be held liable for inducing others to directly infringe, or contributing to direct infringement, by the manufacturing and selling of their drug products with proposed labeling that specifically encourages direct infringement (and where the additional requirements are met). *See id.* at 1364-65. Thus, the infringement inquiry for a method of treatment patent focuses on the use that is described in Defendants’ proposed labeling. *Id.*

#### **IV. Defendants Do Not Infringe The ‘209 Patent**

Lilly has the burden of showing that a single actor performs, or at least “controls or directs” the performance of, each and every step of the asserted claims of the ‘209 patent. Lilly cannot meet this burden. As properly construed, the term “administering” in the ‘209 patent claims requires putting the substance at issue on or into the patient’s body. While the physician

(or other healthcare professionals under his or her control) will perform the administration of intravenous pemetrexed and injection of vitamin B12, it is the patient who self-administers a folic acid pill or multivitamin by ingesting it in accordance with Defendants' proposed labeling.

Defendants expect Lilly will argue for a broader, unsupported, construction of the term "administering" or "administration" in the '209 patent. Lilly's expert, Dr. Chabner, suggested that "administering" is broad enough to encompass prescribing or, even more generally, when a doctor "instructs" a patient to take a drug. Such a construction cannot be supported—the administering of a drug or vitamin is distinct from, and narrower than, either prescribing or instructing. Moreover, a physician does not perform the step of "administering" folic acid even under broader uses of the term that Lilly may propose.

Finally, as a last gasp, Lilly may continue to argue (as it did before the Supreme Court's *Akamai* decision) that it can properly combine the conduct of the doctors and the patients to prove infringement. But a physician does not have any "direction or control" over a patient's use of folic acid such that the patient's actions could be attributed to the physician. Judgment of non-infringement is required.

**A. The Term "Administering" In The '209 Patent Claims Requires Pemetrexed, Vitamin B12, And Folic Acid To Be "Put On Or Into The Patient's Body"**

The asserted claims of the '209 patent contain the phrases "[a]dministering," "administered," and/or "administration" (collectively, the "administering" term). Dr. Schulz will explain, consistent with its plain and ordinary meaning to a POSA, the term "administering" in those claims means putting the recited agents (specifically, pemetrexed, folic acid, and vitamin B12) on or into the patient's body. This construction is supported by the claims and specification of the '209 patent, the most relevant evidence in the claim construction analysis.

*Renishaw PLC v. Marposs Societa'per Azioni*, 158 F.3d 1243, 1250 (Fed. Cir. 1998) ("The

construction that stays true to the claim language and most naturally aligns with the patent's description of the invention will be, in the end, the correct construction.”); *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996).

First, as Lilly has argued, the “patient” of the ’209 patent claims is a “human ***undergoing medical treatment***.” D.I. 115 at 9. In order to treat a patient with pemetrexed, the pemetrexed must be put into the patient’s body. If “administering” pemetrexed means anything short of putting pemetrexed into the patient’s body, then the patient may not be “undergoing medical treatment” through the practice of these method claims. Likewise, the ’209 patent describes the purpose of administering folic acid as reducing the toxicity associated with pemetrexed therapy. TX 1 at 3:7-12. But merely instructing a patient to take folic acid, or even writing him or her a prescription, will not reduce toxicity. “Administering” must refer to putting these agents in the patient’s body for the patient to be treated or be “undergoing medical treatment.”

Second, the ’209 patent claims and the specification of the ’209 patent consistently use the term “administering” in reference to the physical act of putting medication into a patient’s body, *i.e.*, the dose, route, and/or schedule of administration for pemetrexed, folic acid, and vitamin B12. *See AstraZeneca AB v. Hanmi USA, Inc.*, No. 11-760, 2012 U.S. Dist. LEXIS 175666, at \*14-16 (D.N.J. Dec. 10, 2012) (adopting a construction of “administering” referring to “the means of delivering the medication to an individual,” over a construction also referring to “prescription,” where the term “administration” referred to the claimed “oral” route of administration).<sup>4</sup>

The claims of the ’209 patent only make sense if administering is limited to putting the

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<sup>4</sup> Other cases in which a court adopted a construction of “administering” similar to that proposed by Defendants in this case include *Medical Research Inst. v. Bio-Engineered Supplements & Nutrition, Inc.*, No. 05-417, 2007 U.S. Dist. LEXIS 3576, at \*23 (E.D. Tex. Jan. 12, 2007); *Schering Corp. v. Mylan Pharms., Inc.*, No. 09-6383, 2011 U.S. Dist. LEXIS 63825, at \*24 (D.N.J. June 15, 2011); and *Novo Nordisk v. Eli Lilly & Co.*, No. 98-643, 1999 U.S. Dist. LEXIS 18690, at \*62 (D. Del. Nov. 18, 1999).

compounds into the body of the patients. The claims specifically call out how the compounds are put into the body (Claim 14—an intramuscular injection; Claim 16—orally); when they are put into the body (Claim 20—1-3 weeks prior to administration of pemetrexed); and how much is put into the body (Claim 12). These claim limitations about administration of the various treatments are specifically directed to details concerning how to put the compounds at issue (pemetrexed, vitamin B12 and folic acid) into the body of the patient. They are not related to a prescription or instructions.

The specification of the '209 patent also repeatedly uses the term “administered” to describe putting the pemetrexed, vitamin B12 or folic acid into the body of the patient.

- The administration of the compounds may be simultaneous as a single composition or as two separate compositions or can be ***administered sequentially*** as separate compositions ***such that an effective amount of the agent first administered is in the patient's body when the second and/or third agent is administered.*** TX 1 at 4:9-14 (emphasis added).
- [F]olic acid is ***administered orally to a mammal about 1 to 3 weeks post administration*** of the methylmalonic acid lowering agent and ***about 1 to about 24 hours prior to the parenteral administration*** of the amount of an antifolate. *Id.* at 6:35-40 (emphasis added).
- Vitamin B12 is ***administered*** as a 1000 µg intramuscular injection ***1-3 weeks prior to treatment with antifolate.*** *Id.* at 8:42-43 (emphasis added) (relating to clinical trial).
- The antifolate is ***administered in four doses over a two week period by rapid intravenous injection.*** *Id.* at 8:46-48 (emphasis added) (relating to clinical trial).

Moreover, the '209 patent teaches the importance of putting folic acid into the patient's body to load folate stores weeks before antifolate treatment to reduce pemetrexed-related toxicities. *See* TX 1 at 6:28-34. If “administering” folic acid refers to when the doctor prescribes or instructs that it be taken by a patient, rather than the time when it is actually put into the patient's body, then the '209 patent's goal of building folate stores prior to administration of the antifolate to prevent toxicity is not achieved. The claimed invention only

makes sense if “administering” is construed as Defendants propose.

Defendants’ plain meaning construction of “administering” is also consistent with how the term is used in the prior art. “[W]hen prior art that sheds light on the meaning of a term is cited by the patentee, it can have particular value as a guide to the proper construction of the term, because it may indicate not only the meaning of the term to persons skilled in the art, but also that the patentee intended to adopt that meaning.” *Kumar v. Ovonic Battery Co.*, 351 F.3d 1364, 1368 (Fed. Cir. 2003) (quoting *Arthur A. Collins, Inc. v. N. Telecom Ltd.*, 216 F.3d 1042, 1045 (Fed. Cir. 2000)). A number of prior art references relating to pemetrexed, including those that were before the Patent Office during the prosecution of the ’209 patent, use the term “administering” to refer to the act of putting an agent, like pemetrexed or folic acid, into a patient’s body, by referring to the dose, route, and/or schedule for that agent:

[T]he feasibility of ***administering folic acid 5 mg daily for 5 days starting 2 days before MTA*** in minimally- and heavily-pretreated pts was evaluated to determine if folic acid supplementation ameliorates the toxic effects of MIA.... TX 912 (Hammond) (emphasis added).

Study JMAB looked at ***administering [pemetrexed] once weekly*** for 4 wk out of every 6, and study BP-00 1 investigated a schedule of daily times five every 21 d. TX 1152 (Shih) at ELAP00243247 (emphasis added).

In the phase I trial investigating this dose (study JMAA), 37 patients were ***administered [pemetrexed] at doses*** ranging from 50-700 mg/m<sup>2</sup>. *Id.* at ELAP00243248 (emphasis added).

The appropriate dose [of pemetrexed] was then withdrawn, diluted in normal saline, and ***administered intravenously over 10 minutes every 3 weeks***. TX 78 (Rusthoven) at DPEM2\_0001186 (emphasis added).

In specifying a particular timeframe for “administering” folic acid or pemetrexed, the prior art similarly uses the word to refer to when the compound is put into the body of the patient.

Lilly’s argument that “administering” is not limited to the physical act of putting agents into or onto the body, but instead would more broadly cover the acts of “prescribing” and

“instructing,”<sup>5</sup> is inconsistent with how the term is used in the patent and the prior art. For example, under Lilly’s construction, the “patient” of the ’209 patent claims may never undergo treatment because merely prescribing an agent or instructing a patient to take an agent does not necessarily result in treatment if the agent never makes it into the patient’s body. By Lilly’s construction, there would be infringement the moment a doctor instructed a patient to follow a certain regimen, even if the patient never took the vitamins or never received pemetrexed.

Further, the specification never uses the term “administering” to refer to the act of “prescribing” or “instructing.” This makes sense because, as other courts have noted, “[t]he act of prescribing is clearly distinct from the subsequent act of administering medication.” *See Abbott*

*Biotechnology Ltd. v. Centocor Ortho Biotech, Inc.*, No. 09-40089, 2011 U.S. Dist. LEXIS 90176, at \*19-20 (D. Mass. Aug. 12, 2011) (“[T]he plain meaning of the phrase ‘administering to the subject’ does not encompass the act of prescribing[.]”); *see also AstraZeneca*, 2012 U.S. Dist. LEXIS 175666, at \*14-16.

Lilly has used the term “administer” to refer to the physical act of putting an agent in a patient’s body, and acknowledged the difference between administering and prescribing, in a nearly identical context. Recognizing the difficulty that would be presented in this case if the Supreme Court ruled in *Akamai* as it did, Lilly filed an amicus brief with the Court arguing that the *en banc Akamai* decision should be affirmed and that indirect infringement should not require that a single actor carry out each step of a method claim.<sup>6</sup> Lilly gave a scenario where multiple parties were required to perform the steps of a method claim:

For example, arguments have been made that even a simple claim directed for

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<sup>5</sup> Defendants’ present understanding of what Lilly claims the term to mean comes from Dr. Chabner’s infringement report, which states that “administration can encompass the concept of ‘administration’ of the treatment—here performed by the physician when he or she *prescribes* the pemetrexed disodium *and instructs* the patient to take folic acid and vitamin B12....” TX 2250 (Chabner Rpt.) at ¶ 38 (emphasis added).

<sup>6</sup> As explained above, the position taken by Lilly was rejected by the Supreme Court.

example to a “method of treating disease X comprising *administering drug Y to a patient in need thereof*,” requires multiple actors to infringe the claim. This is because a physician will be required to diagnose the disease and *write a prescription for a patient* in need thereof, a pharmacist will fill the prescription, and *a patient or another healthcare provider will administer the drug*.

*See* No. 12-786, 2014 WL 1319146, at \*9 (U.S. Apr. 2, 2014) (“Lilly Amicus Brief”; Exhibit A).

Because the above scenario separately refers to the acts of prescribing by the physician and filling the prescription by the pharmacist, the final step of “administering” the drug could only refer to putting the medication into the patient’s body either by the physician (*e.g.*, by injection) or by the patient (*e.g.*, by ingestion). Lilly’s suggestion that the term “administering” can mean the same thing as “prescribing” directly contradicts of Lilly’s previous use of the term in a nearly identical context.

**B. The Use of Defendants’ Respective ANDA Products Will Not Directly Infringe Any Asserted Claims Of The ’209 Patent Because No Single Actor, In Particular No Physician, Will Administer Pemetrexed, Vitamin B12, And Folic Acid, In Accordance With Defendants’ Proposed Labeling**

As discussed below, there can be no direct infringement because Lilly cannot prove that any physician, following Defendants’ proposed labeling, actually performs, or “directs or controls” the performance of, each and every step of the asserted ’209 patent claims.

**1. The Physician Does Not Actually Perform The Claimed Step Of Administering Folic Acid In The ’209 Patent Claims**

The physician will not perform the claimed step of “administering” folic acid in any of the ’209 patent claims. As discussed above, the claim term “administering” in the ’209 patent claims means that the agent is being put into or on the patient’s body. In accordance with Defendants’ proposed labeling, the patient will purchase folic acid in the form of over-counter-medicine or in the form of a multivitamin, and give it to him- or herself. The patient puts folic acid into his or her own body.

Even if the meaning of “administering” were broadened, a physician would still not

perform the step of “administering” folic acid, in accordance with Defendants’ proposed labeling. Although extrinsic and inconsistent with the ’209 patent’s use of the term “administering,” Lilly may suggest that some physicians use the term “administering” more broadly in practice to also encompass (a) the supervision of the taking of a drug, such as in the presence of a physician or his or her staff, (b) the doling out of medication at a physician’s office, or (c) prescribing a drug to a patient. None of these broader uses of “administering” cover the use of folic acid in accordance with Defendants’ proposed labeling, however, because physicians do not hand out folic acid to their patients, physically do not supervise the patient’s ingestion of folic acid, or prescribe folic acid to the patient. Thus, even under a broader construction of “administering,” there would still be no single actor, including the physician, that actually performs all the steps of the asserted claims.

## **2. The Physician Does Not Otherwise Have Direction Or Control Over The Step Of Administering Folic Acid**

Lilly has suggested that even if a patient “administers” folic acid, the physician still directly infringes the ’209 patent claims because “the physician and the patient will jointly practice the claimed method.” TX 2250 (Chabner Rpt.) at ¶ 39. But for a physician to be directly liable for infringement, it is not enough for the physician and patient to “jointly practice” the claimed method. Instead, the physician must have “direction or control” over the patient’s self-administration, *i.e.*, ingestion, of folic acid. “[M]ere ‘arms-length cooperation’” is not enough. *Muniauction*, 532 F.3d at 1329. “Direction or control” can only be shown by demonstrating an agency relationship or contractual arrangement between the physician and patient sufficient to establish that the physician is vicariously liable for the patient’s actions. Lilly cannot show that the physician has “direction or control” over the patient’s administration of folic acid.

**a. There Is No Agency Or Contractual Relationship Sufficient To Establish Vicarious Liability Between The Physician And Patient**

In accordance with Defendants’ proposed labeling, a physician does not have “direction or control” over a patient’s administration of folic acid under the strict standard adopted by the courts for determining when a party’s actions can be attributable to another for purposes of determining direct infringement. Here, the standard could only be met if Lilly demonstrates the existence of an agency relationship or contractual relationship between the physician and the patient sufficient to make the physician vicariously liable for the patient’s actions – in particular, the patient’s administration of folic acid. Lilly cannot do so.

As a general matter, there is no dispute that the doctor-patient relationship is not one where there is a relationship sufficient to establish that the physician is vicariously liable for the patient. In the panel decision in *McKesson Technologies Inc. v. Epic Systems Corp.*, the Federal Circuit found the doctor-patient relationship lacked the required “control or direction”: “A doctor-patient relationship does not by itself give rise to an agency relationship or impose on patients a contractual obligation such that the voluntary actions of patients can be said to represent the vicarious actions of their doctors.” No. 10-1291, 2011 U.S. App. LEXIS 7531, at \*10, 26-27 (Fed. Cir. Apr. 12, 2011), *vacated on other grounds*, *Akamai*, 692 F.3d at 1305-06. The panel also noted that patients “act[] principally for their own benefit and under their own control” (*Id.* at \*11) (citation omitted), and rejected the argument that the doctor-patient relationship was something more than a mere arms-length relationship (*id.* at \*10).

It was precisely because Lilly understood that a doctor does **not** have control or direction over a patient that Lilly urged the Supreme Court to uphold the Federal Circuit decision *Akamai*. In its amicus brief to the Supreme Court, Lilly explained the law: “Under the Federal Circuit’s ‘control or direction’ test as further articulated in *Muniauction, Inc. v. Thomson Corp.*, 532 F.3d

1318 (Fed. Cir. 2008), a physician and patient would likely *not* have the required relationship to directly infringe under section 271(a)” where the physician and patient each perform steps of a claimed method. Ex. A (Lilly Amicus Brief) at \*10 (citations omitted, emphasis added). Indeed, Lilly acknowledged that even though the *McKesson* case was remanded, “the ‘control or direction’ test remain[ed] unchanged in the context of determining infringement under section 271(a).” *Id.* at \*11. Lilly also admitted that “control or direction requires more than the arm’s length interactions within the health care system.” *Id.* at \*10. Any argument by Lilly to the contrary now rings hollow.

There are no facts in this case that warrant an exception to this general rule regarding the physician-patient relationship. In accordance with Defendants’ proposed labeling, the use of Defendants proposed products does not create an agency relationship between the physician and the patient, nor does it create some contractual relationship or joint enterprise such that the physician is vicariously liable for the actions of the patient. It is the patient who chooses whether to take folic acid supplements; how much to take; when to take it; and where to get it. The patient is under no contractual or legal obligation to the physician to do so. *See Move, Inc. v. Real Estate Alliance Ltd.*, 709 F.3d 1120-22 (Fed. Cir. 2013) (noting an absence of “direction or control” by the alleged controlling party where the alleged controlling party did not make the final choices.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]<sup>7</sup>

**b. Even If The Law Did Not Require An Agency Or Contractual Relationship, Lilly Would Still Fail To Show “Direction Or Control”**

Even if the law did not require an agency relationship or contractual obligation to meet the “control or direction” test, Lilly still cannot show that the physician has “direction or control” over the acts of the patients. At most, the physician tries to control a treatment plan by simply instructing the patient to take folic acid. The Federal Circuit has held, however, that “control[ing] access to [a] system and instruct[ing] [others] on its use is not sufficient” to demonstrate “direction or control.” *See Voter Verified, Inc. v. Premier Election Solutions, Inc.*, 698 F.3d 1374, 1384 (Fed. Cir. 2012) (quoting *Muniauction*, 532 F.3d at 1330). Thus, “[g]iving instructions or prompts to the third party in its performance of the steps necessary to complete infringement, or facilitating or arranging for the third-party’s involvement in the alleged infringement, are not sufficient,” and “generally do not establish the type of direction or control necessary for direct infringement.” *Emtel, Inc. v. Lipidlabs, Inc.*, 583 F. Supp. 2d 811, 834-35 (S.D. Tex. 2008).

**C. Defendants Will Not Induce Infringement Or Contribute To The Infringement Of Any Of The Asserted Claims Of The ’209 Patent**

As noted above, induced infringement and contributory infringement both require a

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<sup>7</sup> [REDACTED]

predicate finding of direct infringement. Because no single actor performs all the steps of the asserted claims of the '209 patent in accordance with Defendants' proposed labeling, and there is thus no direct infringement, Defendants cannot be liable for induced or contributory infringement of any claim of the '209 patent. *See Akamai*, 134 S. Ct. at 2117.

If a physician did "administer" folic acid to a patient, or entered into some relationship with a patient sufficient to establish "direction or control" for purposes of direct infringement, such action(s) would be a consequence of the physician and/or his or her patient *not* following Defendants' proposed labeling. Under this hypothetical scenario, Defendants would still not be liable for induced infringement because Defendants' proposed labeling does not induce, with specific intent to encourage, a single actor to perform every step of a claimed method (*Akamai*, 134 S. Ct. at 2117), and it does not evidence an "affirmative intent to cause direct infringement" (*DSU Med.*, 471 F.3d at 1306). Nor would Defendants be liable for contributory infringement. The use of Defendants' ANDA products in accordance with their proposed labeling is a substantial noninfringing use because no single actor would perform each and every step of the '209 patent claims. *Supra* pp. 15-19. *See Vita-Mix Corp. v. Basic Holding, Inc.*, 581 F.3d 1317, 1327 (Fed. Cir. 2009) ("[N]on-infringing uses are substantial when they are not unusual, far-fetched, illusory, impractical, occasional, aberrant, or experimental.").

## **V. Conclusion**

For the above reasons, this Court should find that there is no direct or indirect infringement of any of the '209 patent claims.

Respectfully submitted,

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**CERTIFICATE OF SERVICE**

I certify that on January 15, 2015, a copy of the foregoing document was filed electronically. Notice of this filing will be sent to the following parties by operation of the Court's electronic filing system. Parties may access this filing through the Court's system:

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